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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/707,900	11/08/2000	Moon Jong Noh	54751-015	9053
35736	7590	04/13/2005	EXAMINER	
JHK LAW P.O. BOX 1078 LA CANADA, CA 91012-1078			WILSON, MICHAEL C	
			ART UNIT	PAPER NUMBER
			1632	

DATE MAILED: 04/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/707,900

Applicant(s)

NOH ET AL.

Examiner

Michael C. Wilson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 February 2005.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5 and 13-15 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5 and 13-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>2-2-5</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-2-05 has been entered. Claims 1-5 and 13-15 remain pending and under consideration. Applicants have not provided any new arguments.

Priority

Examples III-VI are new in this application (pages 23-25). Example VI is not in parent application 09/702718.

Claim Objections

The "and" in claim 15 should be --or--.

Information Disclosure Statement

The IDS filed 2-2-05 has been considered; however, if applicants believe any of the 54 references are particularly relevant to the claimed invention, please point to such references more specifically.

Claim Rejections - 35 USC § 112 - new matter

Claims 1-5 and 13-15 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

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to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The limitation of treating osteoarthritis with chondrocytes transfected with TGF- β 1 or BMP remains new matter (claims 1 and 13). Support has not been provided and cannot be found.

The phrase "transfected/transduced" remains new matter. Support has not been provided and cannot be found (claims 1, 4, 5 and 13).

Failure to provide support for future amendments will be considered non-responsive.

Claim Rejections - 35 USC § 112 - enablement

Claims 1-5 and 13-15 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transfecting fibroblasts with DNA encoding TGF- β 1 operably linked to a promoter, transplanting the transfected fibroblasts into a joint space of a mammal such that expression of TGF- β 1 occurs resulting in generating hyaline cartilage, does not reasonably provide enablement for using chondrocytes encoding TGF- β 1 or BMP to treat arthritis or regenerate any connective tissue as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The specific combination of vector, cell and modes of delivery required to target a desired tissue and regenerate tissue *in vivo* is unpredictable. Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art that show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates, "among the design hurdles for all vectors are the need to increase the

efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

More specifically, at the time of filing Naughton taught transplanting foreskin fibroblasts to a site of cartilage damage in the presence of scaffolding and regenerating cartilage, suggested transfecting the cells with a vector encoding TGF- β 1 and suggested delivering the cells intraarticularly (Naughton, claim 1; col. 10, line 58; col. 4, line 65; col. 13, line 60 - col. 16, line 33; col. 2, line 56 and col. 18, lines 8-42 which discusses administering the cells to joints that have damaged cartilage). Ikeda taught administering a vector encoding TGF- β 1 intraarticularly to obtain TGF- β 1 expression (pg 1667, col. 1, 3rd para.; pg 1669, col. 2). van Beuningen taught TGF- β 1 administered intraarticularly generates articular cartilage (pg 307, col. 1, "intraarticular injections"; pg 308, col. 1, "stimulation of articular cartilage"). The art did not teach how to use fibroblasts or TGF- β 1 to regenerate ligaments or tendons. The art did not teach how to use BMP to regenerate cartilage. The art did not teach how to use osteoblasts or chondrocytes to regenerate cartilage or any other connective tissue.

The specification does not enable using the instant invention to treat osteoarthritis (claim 1). Arthritis in humans causes a diverse T-cell population response against not just collagen or one antigen, but a large number of undefined antigens in the arthritic joint (Fox et al., July 1995, Am. J. Med., Vol. 99, pgs 82-88; pg 87, col. 1, para. 1; pg 84, col. 4, para. 1). The specification demonstrates the invention in rabbits having cartilage defects made with a knife (pg 29, line 7). These rabbits are not an art-accepted model for osteoarthritis; nor do the rabbits correlate to osteoarthritis. While

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arthritic joints require cartilage regeneration, removing cartilage reflect with a knife does not reflect the complex immune response in an arthritic joint. The specification does not teach how damaging cartilage with a knife reflects the diverse T-cell response against the undefined antigens in the arthritic joint as taught by Fox et al. The specification does not provide adequate guidance to regenerate cartilage in an arthritic joint because the cells administered may be attacked by the immune system and may not target the damaged area of cartilage.

The specification does not enable using chondrocytes transfected with DNA encoding TGF- β 1 or BMP to regenerate cartilage or connective tissue. Specifically, the specification does not correlate the results obtained using TGF- β 1 to BMP-2, -3, -4, -5, -6 or -7 such that cartilage would be regenerated. Nor does the specification correlate the function of TGF- β 1 to BMP-2, -3, -4, -5, -6 or -7 such that cartilage could be regenerated. While the specification suggests using BMP (page 11, line 9), the activities and functions of TGF- β 1 and BMPs vary. The specification does not provide the structural features or functional activity of any BMP required to regenerate cartilage or any other connective tissue. The specification does not correlate the results obtained using fibroblasts to chondrocytes. The specification does not correlate the structure or function of fibroblasts and chondrocytes. Without such guidance, it would require one of skill undue experimentation to use different cells and DNA to regenerate connective tissue in view of the state of the art at the time of filing which only taught fibroblasts encoding TGF- β 1.

Given the unpredictability in the art taken with the guidance provided in the specification, it would have required one of skill undue experimentation to use chondrocytes transfected with DNA encoding TGF- β 1 or BMP to regenerate hyaline cartilage or any desired connective tissue as broadly claimed.

Claim Rejections - 35 USC \S 112 - indefiniteness

Claims 1-5 and 13-15 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

The phrase "transfected/transduced" is unclear. The metes and bound of "transfected" and "transduced" cannot be determined. Therefore, the metes and bounds of cells that are either transfected" and "transduced" cannot be determined. The distinction between transfecting and transducing cannot be determined.

The phrase "chondrocyte cells" is indefinite. Chondrocytes are simply referred to as chondrocytes, not chondrocyte cells.

Double Patenting

Claims 1-5 and 13-15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,797,703, application number 09/702,718. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. The claims of the instant application require regenerating connective tissue by transfecting chondrocytes with a viral or plasmid vector encoding TGF- β 1 or BMP

and transplanting the cells by intraarticular injection into an osteoarthritic joint space of a mammal. The claims of '718 require generating hyaline cartilage by transfecting chondrocytes with a viral or plasmid vector encoding TGF- beta1 and transplanting the cells by into the joint space of a mammal. Upon review of the disclosure of '718, the claims in this application could have been claimed during prosecution of '718.

Claim Rejections - 35 USC § 103

Claims 1-5 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton (US Patent 5,842,477, Dec. 1, 1998) in view of Ikeda (Sept. 1998, J. Rheumatol., Vol. 25, pages 1666-1673) and van Beuningen (Sept. 1998, Osteoarthritis and Cartilage, Vol. 6, pages 306-317) for reasons of record.

It is noted that the rejection of claims 1-5 and 13-15 over Naughton, Ikeda and van Beuningen was withdrawn because the references do not teach transplanting cells without scaffolding as newly amended (see the final office action sent 1-24-03, pg 9). However, only claims 13-15 were limited to transplanting cells without scaffolding. Therefore, claims 1-5 remain rejected for reasons of record under 103 because they encompass transplanting cells with or without scaffolding.

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the

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application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service

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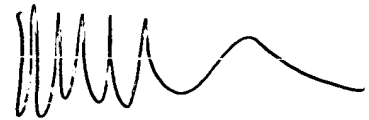
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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

A handwritten signature in black ink, consisting of several vertical strokes followed by a wavy line.

MICHAEL WILSON
PRIMARY EXAMINER